



General

Guideline Title

Pharmacological therapy for acute spinal cord injury. In: Guidelines for the management of acute cervical spine and spinal cord injuries.

Bibliographic Source(s)

Hurlbert RJ, Hadley MN, Walters BC, Aarabi B, Dhall SS, Gelb DE, Rozzelle CJ, Ryken TC, Theodore N. Pharmacological therapy for acute spinal cord injury. In: Guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery. 2013 Mar;72(Suppl 2):93-105. [33 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The rating schemes used for the strength of the evidence (Class I-III) and the levels of recommendations (Level I-III) are defined at the end of the "Major Recommendations" field.

Recommendations

Level I

- Administration of methylprednisolone (MP) for the treatment of acute spinal cord injury (SCI) is not recommended. Clinicians considering MP therapy should bear in mind that the drug is not Food and Drug Administration (FDA) approved for this application. There is no Class I or Class II medical evidence supporting the clinical benefit of MP in the treatment of acute SCI. Scattered reports of Class III evidence claim inconsistent effects likely related to random chance or selection bias. However, Class I, II, and III evidence exists that high-dose steroids are associated with harmful side effects including death.
- Administration of GM-1 ganglioside (Sygen) for the treatment of acute SCI is not recommended.

Summary

Methylprednisolone

Despite 4 prospective blinded randomized controlled trials investigating the effect of MP in acute SCI, there exists no Class I medical evidence of any beneficial effect. Two prospective Class II trials also failed to demonstrate the therapeutic efficacy of MP in SCI. In total, over 980 patients have received steroids for SCI and over 280 have participated as control subjects within the protocol of a prospective clinical trial—in which, universally, all primary comparisons to establish efficacy have been negative.

A variety of Class III medical evidence has been published supporting the neuroprotective effect of MP in SCI. In general, these studies suffer from 1 of 2 significant limitations: limited sample size derived retrospectively from much larger study populations and/or incomplete data reporting in which omitted data are likely to have negated the proposed beneficial effect. Additionally, the beneficial effects claimed related to MP administration in the setting of acute SCI have been inconsistent. Patients are reported to have demonstrated improvement in sensory but not motor function, motor but not sensory function, or some other (undefined) type of neurological recovery. It is important to note that none of these retrospective data analyses have claimed neurological improvement of a meaningful functional or behavioral nature. In light of both significant methodological errors and inconsistent neurological outcomes, the beneficial effects of MP can as easily be ascribed to random chance as to any true therapeutic effect.

Harmful side effects of MP administration in the setting of acute SCI have been reported as significant in 3 Class I studies, including wound infection, hyperglycemia requiring insulin administration, and gastrointestinal (GI) hemorrhage. Although not statistically significant, similar trends were observed in Class I medical evidence from National Acute Spinal Cord Injury Study (NASCIS) II and III, including GI hemorrhage, sepsis, pneumonia, and death due to respiratory failure. In addition, Class II medical evidence shows a significantly higher risk of infection (respiratory, urinary, wound) and steroid-induced myopathy in patients treated with MP compared to controls. Several Class III medical evidence studies describe similar adverse events of statistical significance including pneumonia, respiratory failure, peptic ulcer disease, GI hemorrhage, and hyperglycemia requiring insulin administration. Most compelling is the Class I medical evidence from over 10,000 patients with head injury, indicating that high-dose MP administration leads to significantly higher mortality independent of injury severity.

In summary, there is no consistent or compelling medical evidence of any class to justify the administration of MP for acute SCI. Both consistent and compelling Class I, II, and III medical evidence exists suggesting that high-dose MP administration is associated with a variety of complications including infection, respiratory compromise, GI hemorrhage, and death. MP should not be routinely used in the treatment of patients with acute SCI.

GM-1 Ganglioside (Sygen)

Found indigenously in cell membranes of mammalian central nervous system tissue, GM-1 ganglioside is a compound thought to have antiexcitotoxic activity, promote neuritic sprouting, potentiate the effects of nerve growth factor, and prevent apoptosis. In 1991, a research group reported promising results of a pilot study investigating its use in acute SCI. All patients received a 250 mg bolus of MP followed by 125 mg every 6 hours for 72 hours. GM-1 patients were administered 100 mg of GM-1 per day for 18 to 32 days, with the first dose provided within 72 hours of injury. Neurological assessment was accomplished with American Spinal Injury Association (ASIA) motor score assessments and the Frankel scale.

Of 37 patients entered into the study, 34 were available for 1-year follow up (16 GM-1 patients, 18 placebo). GM-1 ganglioside-treated patients showed significant improvement in Frankel grade from baseline to 1-year follow-up ($P = .034$) and significantly greater improvement in ASIA motor scores compared to placebo-treated patients ($P = .047$). The recovery of motor function in GM-1 ganglioside-treated patients was felt to be due to recovery of strength in paralyzed muscles rather than strengthening of paretic muscles. There were no adverse effects attributed to the administration of the study drug. The authors concluded that GM-1 ganglioside enhanced neurological recovery in human patients following SCI and deserved further study.

The subsequent multicenter study involved 28 neurotrauma institutions and randomized 797 patients within 72 hours of injury to receive either GM-1 ganglioside (100 or 200 mg intravenously [i.v.]/day) or placebo for a total of 56 days. All patients received NASCIS II doses of MP within 8 hours of injury. The duration of follow up was 1 year. Although patients with ASIA grade C and D SCI treated with Sygen demonstrated statistically significant improvement in modified Benzel grade compared to placebo-treated patients at 4 and 8 weeks after injury, the advantage was lost at subsequent follow-up visits. No difference between actively treated and placebo-treated patients was noted in any of the outcome measures at 1 year. There have been no further studies to confirm or refute these results in the last decade. Consequently, GM-1 ganglioside is not recommended for use in the routine management of patients with acute SCI at this time.

Definitions:

Rating Scheme for the Strength of the Evidence: Modified North American Spine Society Schema to Conform to Neurosurgical Criteria as Previously Published and for Ease of Understanding and Implementation: Levels of Evidence for Primary Research Question^a

| Class | Therapeutic Studies: Investigating the Results of Treatment | Diagnostic Studies: Investigating a Diagnostic Test | Clinical Assessment: Studies of Reliability and Validity of Observations, Including Clinical Examination, Imaging Results, and Classifications |
|-------|---|--|--|
| I | High-quality randomized controlled trial with statistically significant | Testing of previously developed diagnostic criteria on | Evidence provided by 1 or more well-designed clinical studies in which interobserver and intraobserver |

| Class | Therapeutic Studies: Investigating the Results of Treatment difference or no statistically significant difference, but narrow confidence intervals | Diagnostic Studies: Investigating a Diagnostic Test consecutive patients (with universally applied reference "gold" standard) | Clinical Assessment: Studies of Reliability and Validity of Observations, Including Clinical Examination, Imaging Results, and Classifications reliability is represented by a \bar{A} , statistic ≥ 0.60 or an intraclass correlation coefficient of ≥ 0.70 |
|-------|--|---|--|
| | Systematic review ^b of Class I randomized controlled trials (and study results were homogeneous ^c) | Systematic review ^b of Class I studies | |
| II | Lesser-quality randomized controlled trial (e.g., <80% follow-up, no blinding, or improper randomization) | Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) | Evidence provided by 1 or more well-designed clinical studies in which interobserver and intraobserver reliability is represented by a \bar{A} , statistic of 0.40–0.60 or an intraclass correlation coefficient of 0.50–0.70 |
| | Prospective ^d comparative study ^e | Systematic review ^b of Class II studies | |
| | Systematic review ^b of Class II studies or Class I studies with inconsistent results | Study of nonconsecutive patients; without consistently applied reference "gold" standard | |
| | Case-control study ^g | Systematic review ^b of Class III studies | |
| | Retrospective ^f comparative study ^e | Case-control study | |
| | Systematic review ^b of Class II studies | | |
| III | Case series ^h | Poor reference standard | Evidence provided by 1 or more well-designed clinical studies in which interobserver and intraobserver reliability is represented by a \bar{A} , statistic of <0.40 or an intraclass correlation coefficient of <0.50 |
| | Expert opinion | Expert opinion | |

^aA complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.

^bA combination of results from 2 or more prior studies.

^cStudies provided consistent results.

^dStudy was started before the first patient enrolled.

^ePatients treated 1 way (e.g., halo vest orthosis) compared with a group of patients treated in another way (e.g., internal fixation) at the same institution.

^fThe study was started after the first patient was enrolled.

^gPatients identified for the study on the basis of their outcome, called "cases" (e.g., failed fusion), are compared with those who did not have outcome, called "controls" (e.g., successful fusion).

^hPatients treated 1 way with no comparison group of patients treated in another way.

Levels of Recommendation

| | |
|-----------|---|
| Level I | Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials) |
| Level II | Recommendations for patient management which reflect moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence) |
| Level III | Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion) |

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Acute spinal cord injury

Guideline Category

Management

Treatment

Clinical Specialty

Critical Care

Neurological Surgery

Neurology

Orthopedic Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To build on the foundation of a previously published medical evidence-based guideline on the use of methylprednisolone (MP) and GM-1 ganglioside in the setting of acute cervical spinal cord injury (SCI), adding pertinent new evidence accumulated over the past decade

Target Population

Patients with acute spinal cord injury (SCI)

Interventions and Practices Considered

Methylprednisolone therapy (MP) and GM-1 ganglioside therapy were considered but not recommended for treatment of acute spinal cord injury (SCI)

Major Outcomes Considered

- Neurological improvement/outcome
- Improvement in motor and sensory scores
- Adverse effects of therapy
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search Criteria

A National Library of Medicine (PubMed) computerized literature search from 1966 to 2011 was undertaken using Medical Subject Headings of "steroids," "methylprednisolone," and "GM-1 ganglioside" in combination with "spinal cord injury" and "neurological deficit." Approximately 680,000 citations were acquired. Non-English-language citations were excluded, as were nonhuman experimental studies. Titles and abstracts of 641 manuscripts were reviewed, 589 on the topic of steroids and human spinal cord injury (SCI) and 52 on the topic of GM-1 ganglioside and human SCI. Additional publications were cross-referenced from the citation lists of the remaining papers. Finally, the members of the author group were asked to contribute articles known to them on the subject matter that were not found by other search means. Duplications, case reports, pharmacokinetic reports, general reviews, editorials, critiques, and manuscripts with mention of one agent or another but without original data were eliminated.

Number of Source Documents

Twenty-seven studies on methylprednisolone (MP) and 2 studies on GM-1 ganglioside provide the basis for this review and are summarized in Evidentiary Table format (refer to Tables 1 and 2 in the original guideline document).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Rating Scheme for the Strength of the Evidence: Modified North American Spine Society Schema to Conform to Neurosurgical Criteria as Previously Published and for Ease of Understanding and Implementation: Levels of Evidence for Primary Research Question^a

| Class | Therapeutic Studies: Investigating the Results of Treatment | Diagnostic Studies: Investigating a Diagnostic Test | Clinical Assessment: Studies of Reliability and Validity of Observations, Including Clinical Examination, Imaging Results, and Classifications |
|-------|---|--|--|
| I | High-quality randomized controlled trial with statistically significant difference or no statistically significant difference but narrow confidence intervals | Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) | Evidence provided by 1 or more well-designed clinical studies in which interobserver and intraobserver reliability is represented by a \bar{A} statistic ≥ 0.60 or an intraclass correlation coefficient of ≥ 0.70 |
| | Systematic review ^b of Class I randomized controlled trials (and study results were homogeneous ^c) | Systematic review ^b of Class I studies | |
| II | Lesser-quality randomized controlled trial (e.g., <80% follow-up, no | Development of diagnostic criteria on consecutive patients | Evidence provided by 1 or more well-designed clinical studies in which interobserver and intraobserver |

| Class | Therapeutic Studies: Investigating the Results of Treatment blinding, or improper randomization) Prospective ^d comparative study ^e | Diagnostic Studies: Investigating a Diagnostic Test (with universally applied reference "gold" standard) Systematic review ^b of Class II studies | Clinical Assessment: Studies of Reliability and Validity of Observations, Including Clinical Examination, Imaging Results, and Classifications reliability is represented by a $\bar{\alpha}$ statistic of 0.40–0.60 or an intraclass correlation coefficient of 0.50–0.70 |
|-------|--|--|---|
| | | | |
| | Systematic review ^b of Class II studies or Class I studies with inconsistent results | Study of nonconsecutive patients; without consistently applied reference "gold" standard | |
| | Case-control study ^g | Systematic review ^b of Class III studies | |
| | Retrospective ^f comparative study ^e | Case-control study | |
| | Systematic review ^b of Class II studies | | |
| | | | |
| III | Case series ^h | Poor reference standard | Evidence provided by 1 or more well-designed clinical studies in which interobserver and intraobserver reliability is represented by a $\bar{\alpha}$ statistic of <0.40 or an intraclass correlation coefficient of <0.50 |
| | Expert opinion | Expert opinion | |

^aA complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.

^bA combination of results from 2 or more prior studies.

^cStudies provided consistent results.

^dStudy was started before the first patient enrolled.

^ePatients treated 1 way (e.g., halo vest orthosis) compared with a group of patients treated in another way (e.g., internal fixation) at the same institution.

^fThe study was started after the first patient was enrolled.

^gPatients identified for the study on the basis of their outcome, called "cases" (e.g., failed fusion), are compared with those who did not have outcome, called "controls" (e.g., successful fusion).

^hPatients treated 1 way with no comparison group of patients treated in another way.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Selected articles were carefully reviewed by the authors. Evidentiary tables were created (refer to Tables 1 and 2 in the original guideline document) that reflected the strengths and weaknesses of each article.

On occasion, the assessed quality of the study design was so contentious and the conclusions so uncertain that the guideline authors assigned a lower medical evidence classification than might have been expected without such a detailed review. In every way, adherence to the Institute of Medicine's criteria for searching, assembling, evaluating, and weighing the available medical evidence and linking it to the strength of the recommendations presented in this document was carried out.

Articles that did not achieve immediate consensus among the author group were discussed extensively until a consensus was reached. Very few contributions required extensive discussion. Most articles were easily designated as containing Class I, II, or III medical evidence using the criteria set forth by the author group at the initiation of the literature evaluation process (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The current author group was selected for its expertise in spinal surgery (both neurosurgical and orthopedic), neurotrauma, clinical epidemiology, and, in several cases, prior experience with guideline development. The topics chosen for inclusion in this iteration of these guidelines are contemporary and pertinent to the assessment, evaluation, care, and treatment of patients with acute cervical spine and/or spinal cord injuries.

Rating Scheme for the Strength of the Recommendations

Levels of Recommendation

| | |
|-----------|---|
| Level I | Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials) |
| Level II | Recommendations for patient management which reflect moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence) |
| Level III | Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion) |

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate pharmacological therapy for acute spinal cord injury

Potential Harms

High-dose methylprednisolone (MP) is associated with a variety of complications including infection, respiratory compromise, gastrointestinal hemorrhage, and death. MP should not be routinely used in the treatment of patients with acute spinal cord injury.

Qualifying Statements

Qualifying Statements

- Medical evidence-based guidelines are not meant to be restrictive or to limit a clinician's practice. They chronicle multiple successful treatment options (for example) and stratify the more successful and the less successful strategies based on scientific merit. They are not absolute, "must be followed" rules. This process may identify the most valid and reliable imaging strategy for a given injury, for example, but because of regional or institutional resources, or patient co-morbidity, that particular imaging strategy may not be possible for a patient with that injury. Alternative acceptable imaging options may be more practical or applicable in this hypothetical circumstance.
- Guidelines documents are not tools to be used by external agencies to measure or control the care provided by clinicians. They are not medical-legal instruments or a "set of certainties" that must be followed in the assessment or treatment of the individual pathology in the individual patients we treat. While a powerful and comprehensive resource tool, guidelines and the recommendations contained therein do not necessarily represent "the answer" for the medical and surgical dilemmas faced with many patients.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Hurlbert RJ, Hadley MN, Walters BC, Aarabi B, Dhall SS, Gelb DE, Rozzelle CJ, Ryken TC, Theodore N. Pharmacological therapy for acute spinal cord injury. In: Guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery. 2013 Mar;72(Suppl 2):93-105. [33 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Mar

Guideline Developer(s)

American Association of Neurological Surgeons - Medical Specialty Society

Congress of Neurological Surgeons - Professional Association

Source(s) of Funding

Congress of Neurological Surgeons

Guideline Committee

Guidelines Author Group of the Joint Section of Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons

Composition of Group That Authored the Guideline

Authors: R. John Hurlbert, MD, PhD, FRCSC, Department of Clinical Neurosciences, University of Calgary Spine Program, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada; Mark N. Hadley, MD (*Lead Author*), Division of Neurological Surgery, University of Alabama at Birmingham, Birmingham, Alabama; Beverly C. Walters, MD, MSc, FRCSC (*Lead Author*), Division of Neurological Surgery, University of Alabama at Birmingham, Birmingham, Alabama, Department of Neurosciences, Inova Health System, Falls Church, Virginia; Bizhan Aarabi, MD, FRCSC, Department of Neurosurgery, University of Maryland, Baltimore, Maryland; Sanjay S. Dhall, MD, Department of Neurosurgery, Emory University, Atlanta, Georgia; Daniel E. Gelb, MD, Department of Orthopaedics, University of Maryland, Baltimore, Maryland; Curtis J. Rozzelle, MD, Division of Neurological Surgery, Children's Hospital of Alabama, University of Alabama at Birmingham, Birmingham, Alabama; Timothy C. Ryken, MD, MS, Iowa Spine & Brain Institute, University of Iowa, Waterloo/Iowa City, Iowa; Nicholas Theodore, MD, Division of Neurological Surgery, Barrow Neurological Institute, Phoenix, Arizona

Financial Disclosures/Conflicts of Interest

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this guideline.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) and EPUB for eBook devices from the [Neurosurgery Web site](#)

Availability of Companion Documents

The following are available:

- Foreword. Guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery 2013;72(3):1. Electronic copies: Available in Portable Document Format (PDF) from the [Neurosurgery Web site](#) .
- Commentary. Guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery 2013;72(3):2-3. Electronic copies: Available in PDF from the [Neurosurgery Web site](#) .
- Introduction to the guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery 2013;72(3):5-16. Electronic copies: Available in PDF from the [Neurosurgery Web site](#) .
- Methodology of the guidelines for management of acute cervical spine and spinal cord injuries. Neurosurgery 2013;72(3):17-21. Electronic copies: Available in PDF from the [Neurosurgery Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 9, 2013. The information was verified by the guideline developer on October 3, 2013.

Copyright Statement

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouse[®] (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the [NGC Inclusion Criteria](#).

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.